Remarks

Claims 11 - 28 are pending. Favorable reconsideration is respectfully solicited.

Claims 11 - 20 have been rejected under 35 U.S.C. § 112 ¶1 as being indefinite. Applicants respectfully traverse this rejection.

The specification, including the claims, is addressed to one of ordinary skill in the art, in this case a chemist skilled in organic synthesis. Applicants have carefully reviewed the specification and claims and do not find any lack of clarity or "indefiniteness". To expedite prosecution, several claim amendments have been made. Each of the Office's contentions regarding indefiniteness will be addressed in turn, numbered as in the Office Action.

1. Silyl protective groups are well known. While the Examiner is correct in that an $-SiH_3$ group is also a silyl group, one skilled in the art of organic synthesis and protective groups views "silyl" as a silicon substituted with three optionally substituted hydrocarbon groups. The most common silyl group is the trimethylsilyl group, due to its lower cost as compared to other silyl groups. The claims have been amended to recite that the silyl groups are $-SiR^4R^5R^6$ groups where R^4, R^5, and R^6 are independently of another an aliphatic or aromatic radical having up to 20 carbon atoms. Support may be found in the specification on page 7, line 35 to page 8, line 2; page 9, lines 30 to 37; and page 12, lines 1 - 20. Examples of these silyl groups are also given.

2. The term "1,3-dicarbonyl compound" is not unclear. This term is widely used in organic chemistry to refer to ß-dicarbonyl compounds. *See, e.g.* the attached paper entitled "Carbonyl Chemistry: 1,3-dicarbonyl compounds". Note that 2,4-pentanedione is described, among other compounds such as ethyl acetoacetate, as a 1,3-dicarbonyl compound. The claim language is clear to one skilled in the art. If the Examiner wishes, Applicants are amenable to amending the claim to recite either "ß-dicarbonyl" or "n,(n+2)-dicarbonyl".

However, Applicants do not believe this to be necessary. Formic anhydride is certainly a 1,3-dicarbonyl compound, as indicated by the formula on page 11, where Y and Z may be H.

3. The Office states that "X as alkoxy or aryloxy in claim 14 is not correct. These are not leaving groups." This is not true. *See* J. March, ADVANCED ORGANIC CHEMISTRY, 3d Ed. p. 315 (attached) which identifies both these as leaving groups. While these are not the best leaving groups, they will perform this function, generally in the presence of acid, *i.e.* in protonated form.

4. The Office further alleges that alkyl (claim 18) is not a leaving group for amine. Reference may be had to *T. Greene, et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, p. 388, which indicates that alkyl groups are leaving groups for amines.

5. The Office alleges that R^1 as alkyl in claim 13 is incorrect as "methyl is not a protective group for hydroxyl". Reference may be had to *Greene, op. cit.*, pp. 14 - 15.

6. Claim 19 has been amended to eliminate "general", which was intended to have been done in the Preliminary Amendment accompanying the National Phase filing. Applicants apologize for this oversight.

7. Claim 20 is believed to be clear. In formula (1) of claim 11, each of R^8, R^9, R^{10}, and R^{11} may be hydrogen. Removal of the protective group R^1 from this compound will generate the compound of formula (6). If the nitrogens also bear protective groups, these will already have been removed prior to removing R^1. If the Examiner wishes, Applicants agree to amend the claim by inserting "and removing any amino protective groups". Please advise if this amendment is viewed as necessary.

Withdrawal of the rejections of the claims under 35 U.S.C. § 112 ¶1 is respectfully solicited.

Claims 14 and 18 have been rejected under 35 U.S.C. § 112 ¶2 as being non-enabling. The claims are addressed to one skilled in the art. One so skilled, particularly in view of numerous scientific articles pertaining to synthesis and cleavage of leaving groups is enabled to make and use the claimed invention. The use of alkoxy and aryloxy leaving groups is known, as evidenced by *March, op. cit.* The same is true regarding claim 18. *See Greene, op. cit.* There is no evidence that cleavage of such leaving groups could not be accomplished without destroying the molecule. If the Office believes this to be the case, a reference should be cited. Applicants have indicated that the groups of claims 14 and 18 are leaving groups. The specification is presumptively accurate. *See, e.g. In re Marzocchi*, 169 USPQ 367 (CCPA 1971). *See* also *In re Soli*, 137 USPQ 797 (CCPA 1963) and *In re Wagner*, 152 USPQ 552 (CCPA 1967) regarding the need for factual evidence in support of such a rejection. Withdrawal of the rejection of claims 14 and 18 under 35 U.S.C. § 112 ¶2 is solicited.

New claims 21 to 26 have been added to more particularly point out and distinctly claim preferred embodiments of Applicants' invention. None of these added claims raise any issue of new matter.

Applicants submit that the claims are now in condition for Allowance, and respectfully request a Notice to that effect. If the Examiner believes that further discussion will advance the prosecution of the Application, the Examiner is highly encouraged to telephone Applicants' attorney at the number given below.

Please charge any fees or credit any overpayments as a result of the filing of this paper to our Deposit Account No. 02-3978.

Respectfully submitted,

Wolfgang Döring et al.

By _____
William G. Conger
Reg. No. 31,209
Attorney/Agent for Applicant

Date: July 28, 2008

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Attachments

CFQ & PP: Carbonyl Chemistry: 1,3-Dicarbonyl Compounds

Reading

Brown and Foote: Sections 17.9, 19.3D and 19.6

Suggested Text Exercises

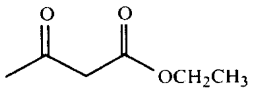
Brown and Foote: Chapter 17: 6
Chapter 19: 11 – 13, 46 - 50

Optional Interactive Organic Chemistry CD and Workbook

Mechanisms: Decarboxylation of a β-Dicarboxylic Acid (p. 23)
Decarboxylation of a β-Ketocarboxylic Acid (p. 24)

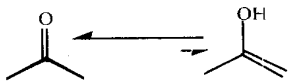
Concept Focus Questions

1. Name and illustrate each of the three fundamental carbonyl mechanism steps using ethyl acetoacetate, a typical 1,3-dicarbonyl compound. Explain why a particular site within the molecule is preferred for this mechanism step.

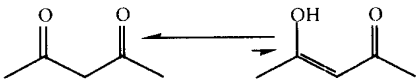


ethyl acetoacetate

2. A carbonyl compound exists in equilibrium with the corresponding enol form. In water, this equilibrium for acetone contains only 2 x 10^{-4} % enol, whereas the enol content for 2,4-pentanedione is 16%. Explain this difference.



2 x 10^{-4}% enol
K_{eq} = 2 x 10^{-6}



16% enol
K_{eq} = 0.19

3. Condensation reactions are the most important synthetic routes to 1,3-dicarbonyl compounds. Illustrate the synthesis of ethyl acetoacetate with a Claisen condensation.

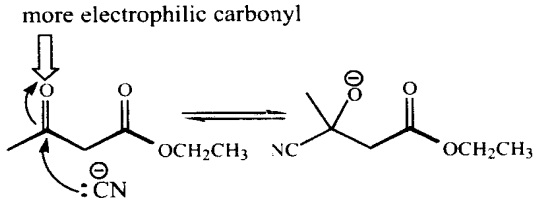
4. What is the synthetic advantage of the acetoacetic ester synthesis? Give a specific example and include a complete mechanism.

5. Briefly discuss the role of the retro-aldol reaction and keto-enol tautomerism in glycolysis. (You may skip this question if glycolysis was not covered in lecture.)

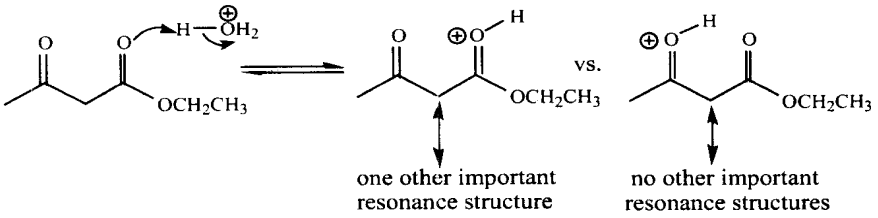
Concept Focus Questions Solutions

1. Review the three fundamental carbonyl mechanism steps from the Fundamentals of Carbonyl Chemistry CFQ if needed.

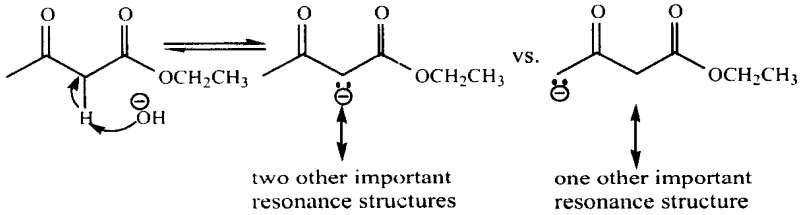
Nucleophilic addition: The nucleophile will add preferentially to the more electrophilic carbonyl first. A ketone carbonyl has a greater charge on the carbonyl carbon, and is thus more electrophilic. (Alternately, the ketone does not lose any resonance when it accepts a nucleophile, whereas the ester loses the minor resonance contributor.)



Electrophilic addition (usually protonation): An ester is more readily protonated than a ketone because the protonated ester that results has more resonance contributors than the protonated ketone.

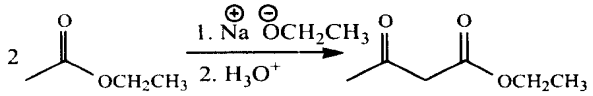


Form an enolate: The most acidic hydrogen is removed first. The most acidic hydrogen atom, upon removal, affords the most stable conjugate base. Deprotonation of the carbon between the two carbonyls yields an enolate with three resonance structures. Deprotonation on the other side of the ketone carbonyl leads to an enolate that has but one other important resonance form, and is thus less stable and harder to form.

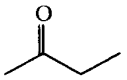
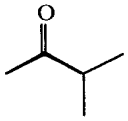


2. The sum of the bond energies for the keto form of acetone is greater than the bond energy sum for the enol form. Thus the keto form is more stable. Conjugation and intramolecular hydrogen bonding are not present in the enol form of acetone, but do stabilize the enol form of 2,4-pentanedione. Because of this, the energy difference between the enol and keto forms of the dione is less than the energy difference between the enol and keto forms of acetone. The keto-enol equilibrium contains a greater percentage of enol when the energy difference between the keto and enol forms is less.

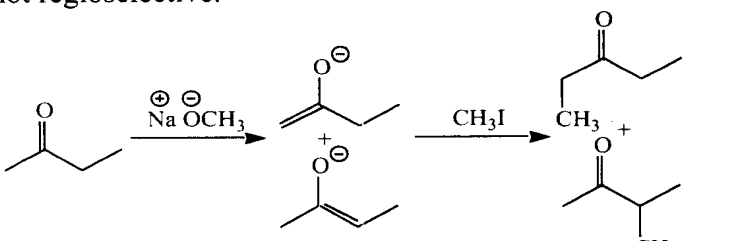
3. A condensation reaction is a reaction in which two or more molecules combine to make a larger molecule with the loss of a small neutral molecule, often water. A condensation of two esters is called the Claisen condensation. Claisen condensation between two molecules of ethyl acetate (via the ester enolate) affords ethyl acetoacetate.



4. The acetoacetic ester synthesis is a protocol for regiospecific alkylation of a ketone. That is, it provides a way to form a new carbon-carbon bond specifically on one side of a ketone carbonyl. The procedure involves a β-ketoester. The ester group serves to direct enolate formation (and thus carbon-carbon bond formation) exclusively to one site, due to differences in acidity. Once the new carbon-carbon bond has been formed, the ester is removed by hydrolysis to the carboxylic acid, and decarboxylation of the β-keto acid.

Example: Convert  into 

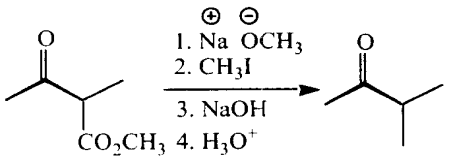
Normal ketone enolate formation and alkylation yields a mixture of products. The reaction is not regioselective.



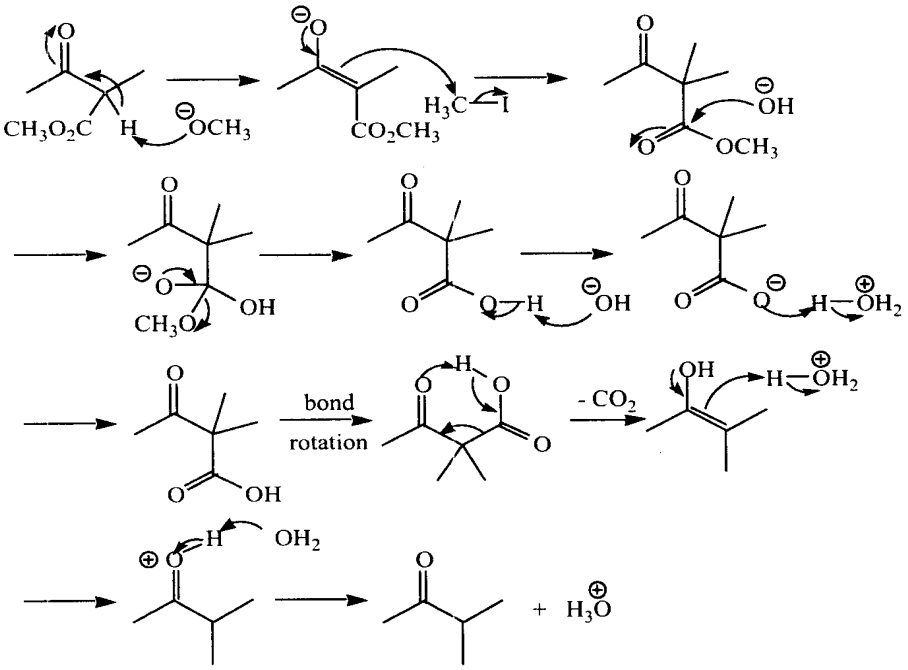
little selectivity in enolate formation

mixture of products

Application of the acetoacetic ester synthesis allows regioselective formation of the desired product.

Overall scheme: 

Mechanism details:

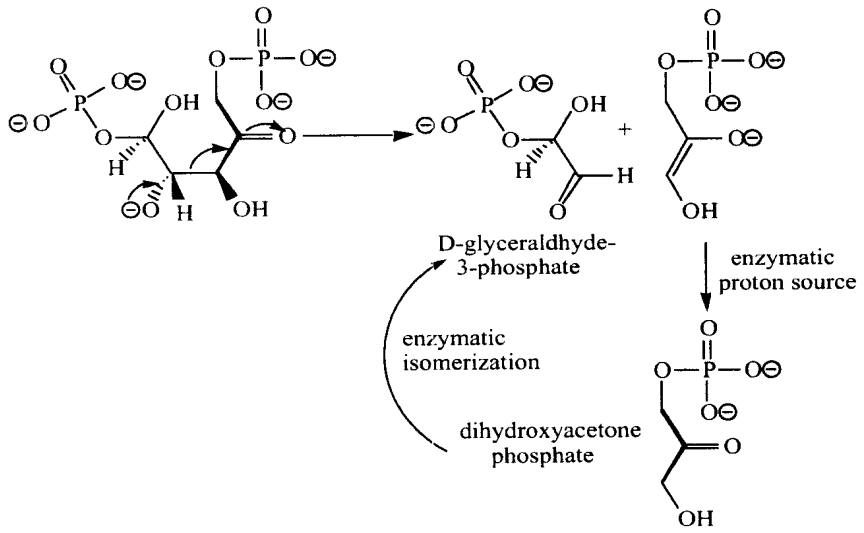


The deprotonation of the intermediate β-ketoacid followed by protonation with H_3O^+ (second line of mechanism scheme) may appear pointless. However, hydroxide is a strong base and carboxylic acid deprotonation cannot be stopped. Thus is it necessary to protonate with acid prior to decarboxylation.

The malonic ester synthesis proceeds is a very similar manner, affording a carboxylic acid product.

The main synthetic advantages of the acetoacetic ester and malonic ester syntheses are mild reaction conditions and excellent control of position of new C-C bond.

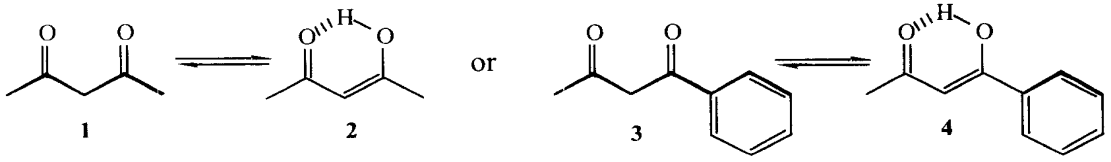
5. Glycolysis is the biological process in which glucose is metabolized. The overall source of energy is the oxidation of C-H and C-C bonds to stronger C-O bonds. A retro-aldol reaction is used to cleave a carbon-carbon bond, affording one molecule each of D-glyceraldehyde-3-phosphate and dihydroxyacetone phosphate.



Further oxidation of D-glyceraldehyde-3-phosphate provides some energy. The dihydroxyacetone phosphate cannot be metabolized as is, and thus represents a waste of half the carbons in a molecule of glucose. However, dihydroxyacetone and glyceraldehyde are isomers. Isomerization of the useless dihydroxyacetone into glyceraldehyde allows this half of the glucose to be used for energy as well. On the surface, this isomerization appears to occur by a simple keto-enol tautomerization process, but in reality, involves a more complex enzymatic mechanism involving the enamine of dihydroxyacetone.

Practice Problems

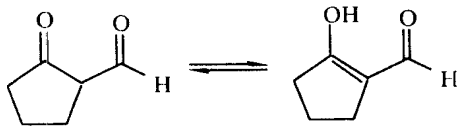
1. Which of the two equilibria shown below will lie furthest to the right? Briefly explain your answer.

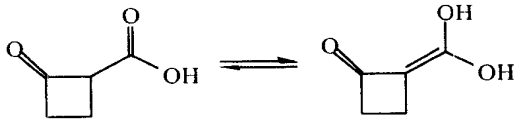


2. Provide a detailed curved arrow mechanism that shows how enol **2** forms from dione **1** in aqueous acid.

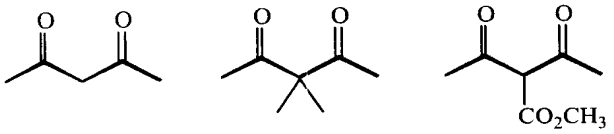
3. Provide a detailed curved arrow mechanism that shows how enol **4** forms from dione **3** in aqueous base.

4. Determine if these equilibria favor the left or right side. Briefly explain.

(a) 

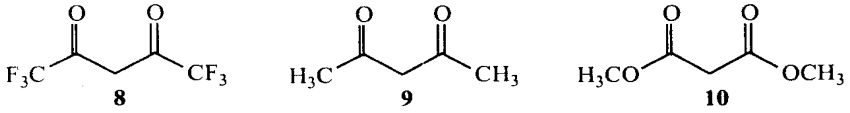
(b) 

5. Rank these 1,3-dicarbonyl compounds by increasing pK_a. Briefly explain.



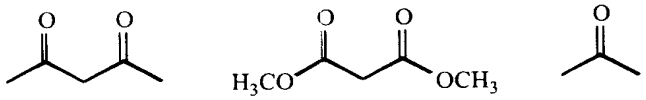
5 **6** **7**

6. Rank these structures in order of increasing acidity. Provide the structure of a dicarbonyl compound which is clearly more acidic than any of these compounds.

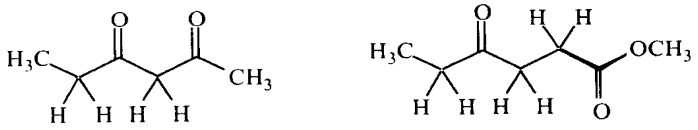


8 **9** **10**

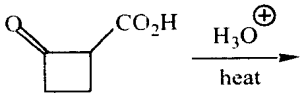
7. Assign a pK_a value of 20, 13 or 9 for each structure. Briefly explain your reasoning.



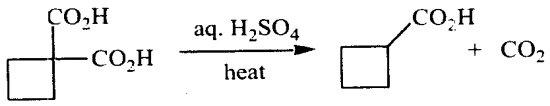
8. Select the single most acidic hydrogen in each molecule.

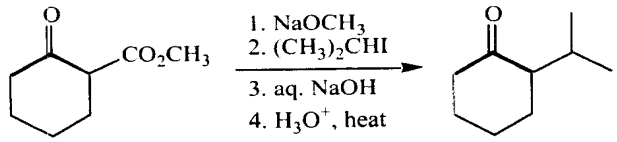


9. Write the organic product(s) and reaction mechanism.

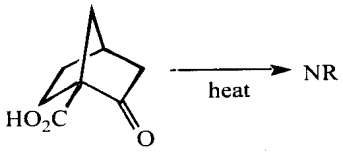


10. Provide mechanisms.

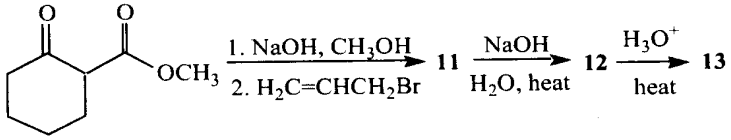
(a) 

(b) 

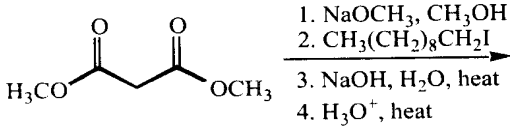
11. The β-ketoacid shown below is stable to heating; it does not lose CO_2. Explain.



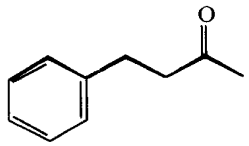
12. Provide the structures of products **11 – 13**.



13. Provide the organic product(s) of the following reaction. If more than one product is formed, indicate which is the major product. If no reaction occurs, write "NR."

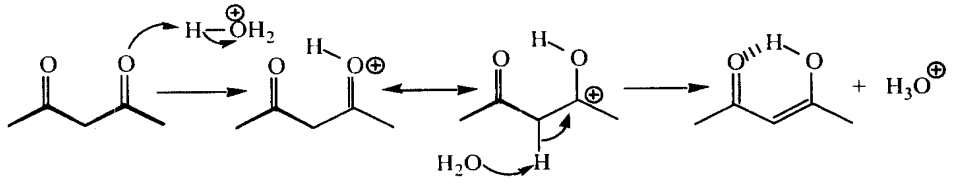


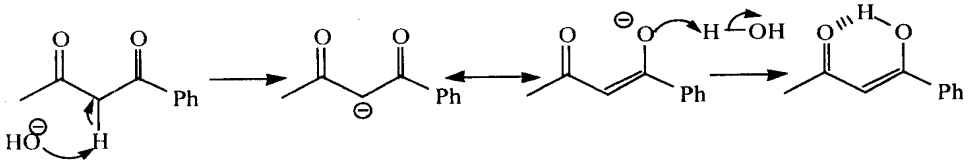
14. Show how the following compounds could be synthesized starting with dimethyl malonate or ethyl acetoacetate, and any other needed reagents.

(a) $Ph(CH_2)_6CO_2H$ (b) 

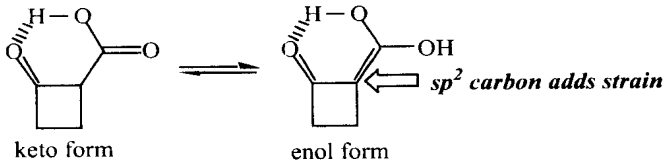
Practice Problems Solutions

1. The formation of an enol from a 1,3-dicarbonyl compound is driven by gain of intramolecular hydrogen bonding and conjugation. Enols **2** and **4** both have one intramolecular hydrogen bond, so this will not be useful in differentiating them. Enol **2** has two conjugated functional groups (the carbonyl and the alkene), whereas enol **4** has three conjugated functional groups (carbonyl, alkene, and benzene ring). Increasing conjugation increases stability. Thus, we predict the second equilibrium to favor the enol more than the first equilibrium.

2. 

3. 

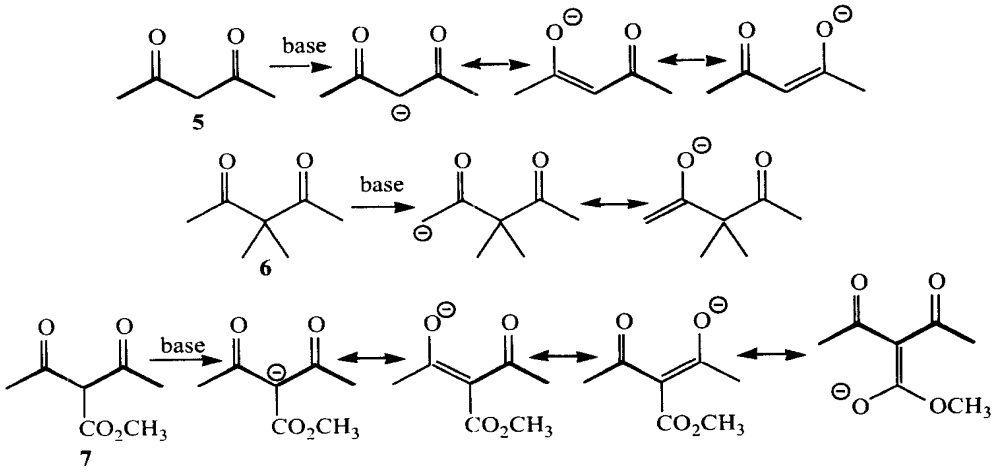
4. (a) The driving force for the formation of the enol tautomer (right side of the equilibrium) is the addition of an intramolecular hydrogen bond, and conjugation of the C=C and C=O. Neither of these stabilizing factors is present in the keto tautomer (left side of the equilibrium). Therefore the equilibrium lies to the right.



(b) The enol form of the carboxylic acid (structure on the right) is conjugated. This is a stabilizing factor that favors the right side of the equilibrium. Both the keto and enol forms of a β-ketoacid can undergo intramolecular hydrogen bonding, so hydrogen bonding will not have a major effect on the position of this equilibrium. However, there is an increase in ring strain due to the addition of a second sp^2 carbon in the cyclobutane ring. If this added strain is greater than the added stability due to conjugation and hydrogen bonding, the equilibrium lies to the left. (Molecular modeling calculations suggest the equilibrium lies to the right by several kcal mol^{-1}, and that the intramolecular =O---H bond distance is too long (about 2.5 Å) to play a significant role. Typical H-bonding distances are 2.0 Å or less.)

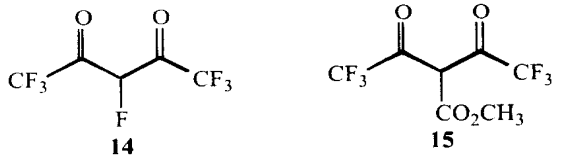
5. pK_a is determined by the stability of the conjugate base. Stability of the conjugate base is determined in this case by the number of resonance contributors. More

resonance contributors result in more stability of conjugate base and thus lower pK_a. The conjugate bases have the following resonance forms:



The enolate from dione **5** has three resonance contributors, the enolate from dione **6** has two resonance contributors, and the enolate from dione (actually trione) **7** has four resonance contributors. Using the reasoning stated above, the pK_a order is: **7** (lowest pK_a) < **5** < **6**.

6. The conjugate bases of all three diones will have the same number of resonance contributors, so resonance is not expected to be a significant difference. The CF_3 group is electron withdrawing. This stabilizes the conjugate base of **8**, making this dione more acidic. Methyl is a mild electron-donating group, causing a small destabilization of the conjugate base of **9**. Methoxy is a strong electron-donating group, causing a greater destabilization of the conjugate base of **10**. Thus, the order of acidity is: (least acidic) **10** < **9** < **8** (most acidic). Any 1,3-dicarbonyl compound with a conjugate base which is more stable than the most stable conjugate base from part (a) will be more acidic. For example, adding more electron-withdrawing groups (compound **14**) or more resonance contributors for the conjugate base (compound **15**) can achieve this.



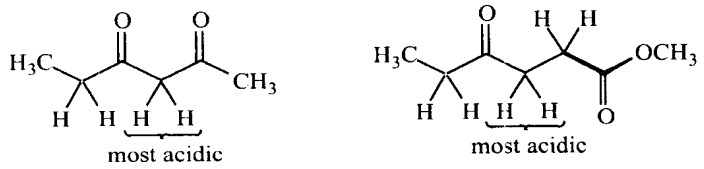
7. A convenient way to consider pK_a is by examining the stability of the conjugate bases. The more stable the conjugate base, the more readily the acid will lose a proton to form it, and thus acid will be more acidic. Factors that stabilize the negative charge of the conjugate base (more resonance contributors, electron-withdrawing groups) will lower pK_a.

Comparing 2,4-pentandione (first structure) with acetone (third structure): Removal of hydrogen atoms from the CH_2 between the two carbonyl groups yields an enolate with three resonance contributors. Deprotonation of acetone affords an enolate with two resonance forms. The enolate derived from 2,4-pentanedione is more stable than the enolate derived from acetone, so the pK_a of 2,4-pentanedione is less than the pK_a of acetone.

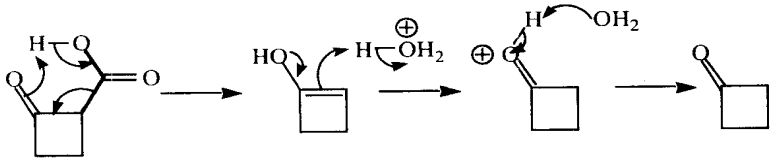
Comparing 2,4-pentanedione with dimethyl malonate (center structure): Both afford enolates with three resonance contributors. The CH_3 groups of 2,4-pentanedione are weak electron donors, so they will reduce the conjugate base stability by a small amount. The methoxy groups of dimethyl malonate are strong electron donors by resonance, so they reduce the stability of the conjugate base by a larger amount.

Therefore the enolate of 2,4-pentanedione is more stable than the enolate of dimethyl malonate, so the pK_a of 2,4-pentanedione is lower than the pK_a of dimethyl malonate. The pK_a assignments are: Acetone pK_a 20, dimethyl malonate pK_a 13, and 2,4-pentanedione pK_a 9.

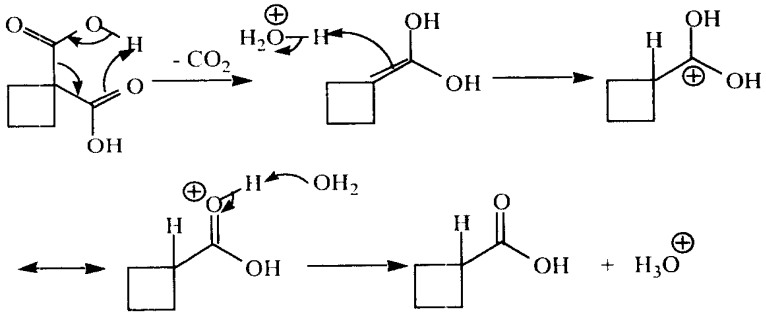
8.



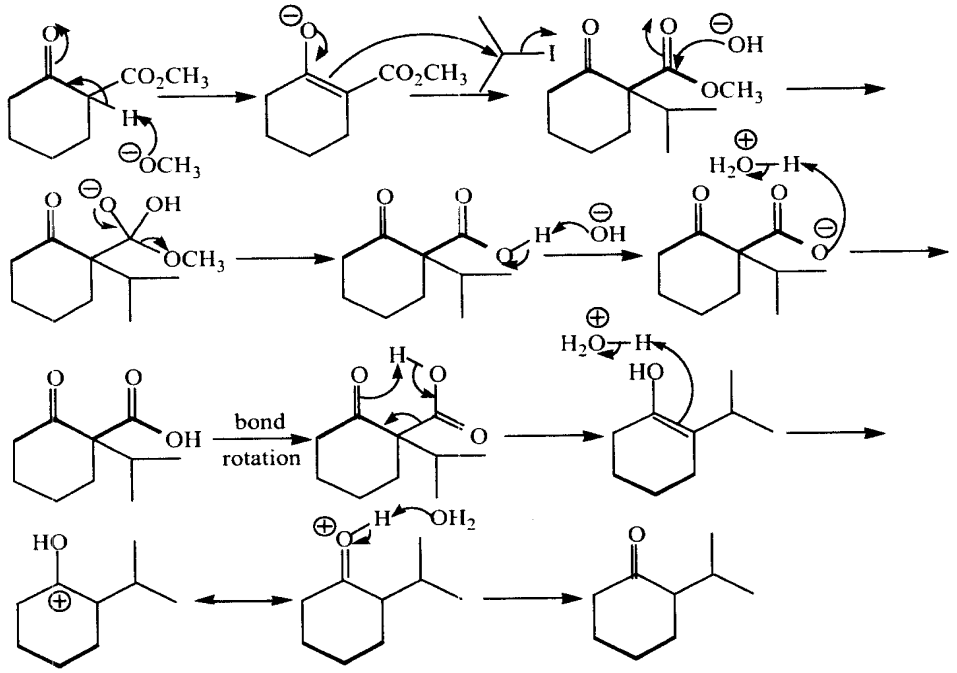
9.



10. (a)

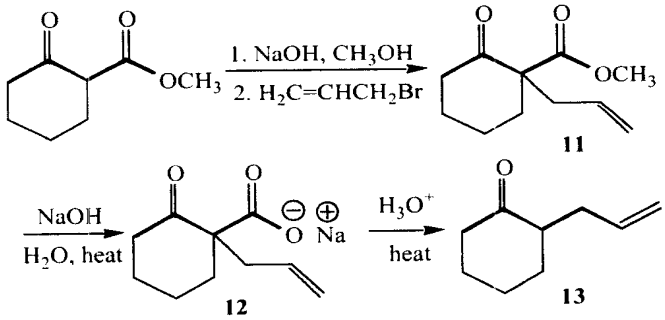


(b)

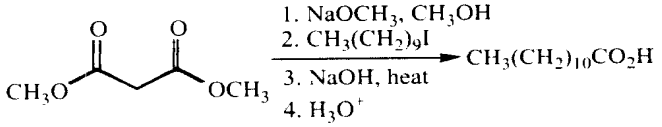


11. Decarboxylation of a β-ketoacid proceeds through an enol. In this case, the enol intermediate shown below has a very strained alkene (make a model). This strain raises the energy of activation leading to the enol enough so that it cannot easily form.

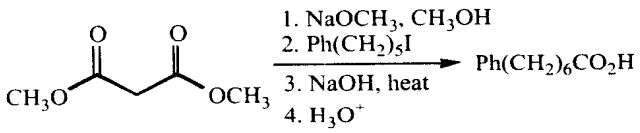
12.



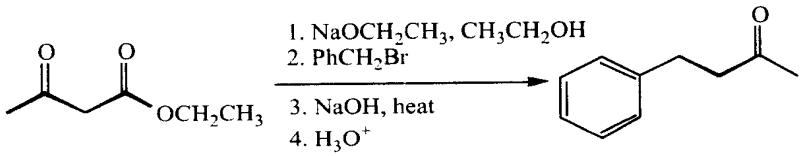
13.



14. (a) Synthesis of a carboxylic acid can be achieved via the malonic ester synthesis.



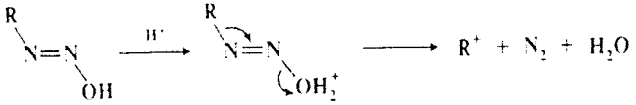
(b) Synthesis of a ketone can be achieved via the acetoacetic ester synthesis.



chemically activated) that can hold their configuration have been postulated,[109] as have ion pairs, in which OH (or OAc, etc., depending on how the diazonium ion is generated) is the counterion.[111]

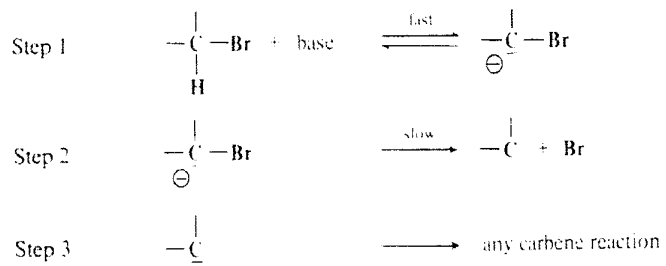
Diazonium ions generated from ordinary aliphatic primary amines are usually useless for preparative purposes, since they lead to a mixture of products giving not only substitution by any nucleophile present, but also elimination and rearrangements if the substrate permits. For example, diazotization of *n*-butylamine gave 25% 1-butanol, 5.2% 1-chlorobutane, 13.2% 2-butanol, 36.5% butenes (consisting of 71% 1-butene, 20% *trans*-2-butene, and 9% *cis*-2-butene), and traces of butyl nitrites.[112]

It has been suggested[113] that the reaction between aliphatic amines and nitrous acid may lead to carbocations *without* the intermediacy of diazonium ions. This could happen if the C—N bond of the diazohydroxide (see p. 571 for the mechanism of diazonium ion formation) is cleaved at the same time as the N—O bond:



There is evidence that changing to a better leaving group in an SN2 reaction causes the newly forming bond between the carbon and the nucleophile to be more fully formed in the transition state, while the bond from the carbon to the leaving group is essentially unchanged.[114]

In the SN1cA and SN2cA mechanisms (p. 311) there is a preliminary step, the addition of a proton, before the normal SN1 or SN2 process occurs. There are also reactions in which the substrate *loses* a proton in a preliminary step. In these reactions there is a carbene intermediate.



Once formed by this process, the carbene may undergo any of the normal carbene reactions (see p. 174). When the net result is substitution, this mechanism may be called the SN1cB (for conjugate base) mechanism.[115] Though the slow step is an SN1 step, the reaction is second order; first order in substrate and first order in base.

Table 10 lists some leaving groups in approximate order of ability to leave. The order of leaving-group ability is about the same for SN1 and SN2 reactions.

2. *At a carbonyl carbon.* In both the SN1 and SN2 mechanisms the leaving group departs during the rate-determining step and so directly affects the rate. In the tetrahedral mechanism at a carbonyl carbon, the bond between the substrate and leaving group is still intact during the slow

[109]Semenow, Shih, and Young, *J. Am. Chem. Soc.* **80**, 3472 (1958). For a review of "hot" or "free" carbocations, see Keating and Skell, Ref. 70d.

[111]Collins, Ref. 80; Collins and Benjamin, *J. Org. Chem.* **37**, 1388 (1972); Collins, Glover, Eckart, Raien, Benjamin, and Benjamin, *J. Am. Chem. Soc.* **94**, 869 (1972); White and Field, *J. Am. Chem. Soc.* **97**, 2138 (1975); Cohen, Botelho, and Jatkowski, *J. Org. Chem.* **45**, 2830 (1980); Cohen, Dvorovetz, and Sidani, *J. Org. Chem.* **45**, 2847 (1980).

[112]Whitmore and Langlois, *J. Am. Chem. Soc.* **54**, 3441 (1932); Streitwieser and Schaeffer, *J. Am. Chem. Soc.* **79**, 2888 (1957).

[113]Chiurdoglu, Bolton, Sichel, Sipos, and Tickle, *J. Chem. Soc.* 2513 (1965); Maccoll, Craig, and Saltiel, *J. Am. Chem. Soc.* 85, 1701 (1963); Maccoll and Wiseman, *J. Chem. Soc., Perkin Trans. 2*, 1965 (1973).

TABLE 10 Leaving groups listed in approximate order of decreasing ability to leave. Groups that are common leaving groups at saturated and carbonyl carbons are indicated

	Common leaving groups	
Substrate RX	**At saturated carbon**	**At carbonyl carbon**
RN_2^+	×	
ROR_2^+		
$ROSO_2C_4F_9$		
$ROSO_2CF_3$	×	
$ROSO_2F$		
ROTs, etc.[117]	×	
RI	×	
RBr	×	
ROH_2^+	× (conjugate acid of alcohol)	
RCl	×	× (acyl halides)
$RORH^+$	× (conjugate acid of ether)	
$RONO_2$, etc.[118]		
RSR_2^+[119]		
RNR_3^+	×	
RF		
ROCOR′[120]	×	× (anhydrides)
RNH_3^+		
ROAr[121]		× (aryl esters)
ROH		× (carboxylic acids)
ROR		× (alkyl esters)
RH		
RNH_2		× (amides)
RAr		
RR		

step. Nevertheless, the nature of the leaving group still affects the reactivity in two ways: (1) By altering the electron density of the carbonyl carbon, the rate of the reaction is affected. The greater the electron-withdrawing character of X, the greater the partial positive charge on C and the more rapid the attack by a nucleophile. (2) The nature of the leaving group affects the *position of equilibrium*. In the intermediate **68** (p. 291) there is competition between X and Y as to which group leaves. If X is a poorer leaving group than Y, then Y will preferentially leave and **68** will revert to the starting compounds. Thus there is a partitioning factor between **68** going on to product (loss of X) or back to starting compound (loss of Y). The sum of these two factors causes the sequence of reactivity to be RCOCl > RCOOCOR′ > RCOOAr > RCOOR′ > RCONH$_2$.

[117]ROTs, etc., includes esters of sulfonic and sulfinic acids.

[118]ROSO$_2$OR, etc., includes inorganic ester leaving groups such as ROPO(OH)$_2$.

[119]For a review of the reactions of sulfonium salts, see Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, 1978, pp. 168–203.

[120]For a review of the reactions of carboxylic acid derivatives, see Gilchrist and Storr, *Organic Reactions and Orbital Symmetry*, Cambridge University Press, Cambridge, 1979, pp. 1–28.

[121]Nitro substitution increases the leaving-group ability of ArO groups, and alkyl picrates (2,4,6-$(NO_2)_3C_6H_2OR$) react at rates comparable to tosylates: Simonetta and Winkler, *J. Chem. Soc. B*, 1065 (1971); Suggitt, Gibbons, Pratt, and Wilson, *J. Chem. Soc., Perkin Trans. 2*, 906 (1972).

9. 1-Adamantyl Carbamate (Adoc–NR_2): R_2NCO_2–1-adamantyl

Formation

1. AdocCl, histidine, NaOH, Na_2CO_3, H_2O, 86% yield; forms N^{α}, N^{im}-Adoc-His(Adoc)OH.[25]

Cleavage

The Adoc group can be cleaved by the same methods used to cleave the BOC group. The Adoc group is somewhat more stable than is the BOC group to acid.

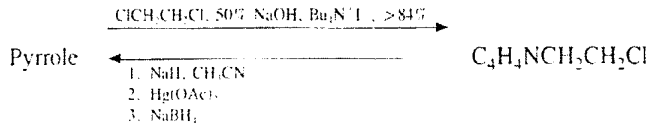
N-Alkyl and *N*-Aryl Derivatives

10. *N*-Vinylamine: $CH_2{=}CH{-}NR_2$

The vinyl group has been used to protect the nitrogen of benzimidazole during metalation with lithium diisopropylamide. It is introduced with vinyl acetate [$Hg(OAc)_2$, H_2SO_4, reflux, 24 h] and cleaved by ozonolysis (MeOH, −78°).[26]

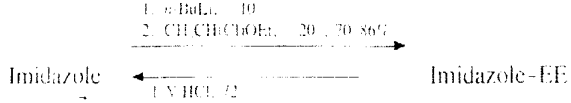
11. *N*-2-Chloroethylamine: $R_2NCH_2CH_2Cl$

Formation/Cleavage[27]



12. *N*-(1-Ethoxy)ethylamine (EE–NR_2): $R_2NCH(OCH_2CH_3)CH_3$

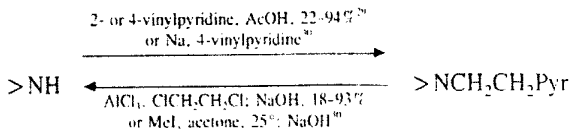
Formation/Cleavage[28]



13. *N*-2-(2′-Pyridyl)ethylamine: $R_2NCH_2CH_2$–2-(C_5H_4N)

14. *N*-2-(4′-Pyridyl)ethylamine: $R_2NCH_2CH_2$–4-(C_5H_4N)

Formation/Cleavage



A series of substituted benzimidazoles and pyrroles was protected and deprotected using this methodology.

N-Trialkylsilylamines

Pyrroles and indoles can be protected with the *t*-butyldimethylsilyl group by treatment with TBDMSCl and *n*-BuLi or NaH.[31] Triisopropylsilyl chloride (NaH, DMF, 0°–rt, 73% yield) has been used to protect the pyrrole nitrogen in order to direct electrophilic attack to the 3-position.[32] It has also been used to protect an indole.[33] This derivative can be prepared from the silyl chloride and K.[34] The silyl protective group is cleaved with $Bu_4N^+F^-$, THF, rt or with CF_3COOH.

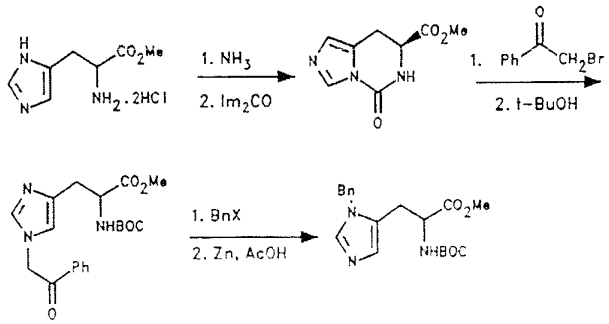
15. *N*-*t*-Butyldimethylsilylamine (R_2N–TBDMS)

16. *N*-Triisopropylsilylamine (R_2N–TIPS)

17. *N*-Benzylamine (Bn–NR_2): $PhCH_2{-}NR_2$

Formation

1. BnCl, NH_3, Na.[35]



The following benzyl halides were used: $PhCH_2Br$, 82% yield; $PhCH(CH_3)Br$, 33% yield; $(Ph)_2CHBr$, 50% yield; 3,4-$(MeO)_2C_6H_3CH_2Cl$, 52% yield.[36]

ETHERS

Ethers are among the most used protective groups in organic synthesis. They vary from the simplest, most robust, methyl ether to the more elaborate, substituted, trityl ethers developed for use in nucleotide synthesis. They are formed and removed under a wide variety of conditions. Some of the ethers that have been used to protect alcohols are included in Reactivity Chart 1.[1]

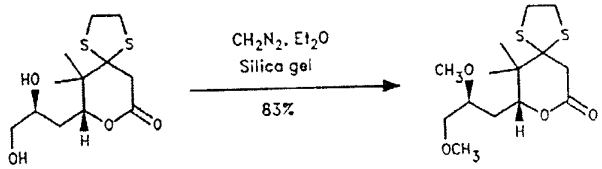
1. See also: C. B. Reese, "Protection of Alcoholic Hydroxyl Groups and Glycol Sys-

New York, 1971, Vol. 10/2, pp. 1001–1044; C. B. Reese, *Tetrahedron*, **34**, 3143–3179 (1978), see pp. 3145–3150; V. Amarnath and A. D. Broom, *Chem. Rev.*, **77**, 183–217 (1977) (see pp. 184–194); M. Lalonde and T. H. Chan, "Use of Organosilicon Reagents as Protective Groups in Organic Synthesis," *Synthesis*, 817 (1985).

1. Methyl Ether: ROMe (Chart 1)

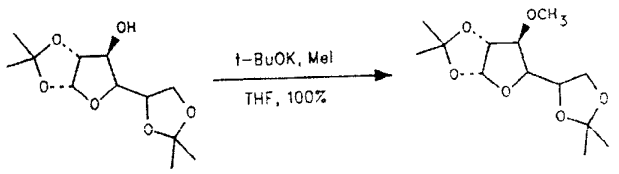
Formation

1. Me_2SO_4, NaOH, $Bu_4N^+I^-$, org. solvent, 60–90% yield.[1]
2. CH_2N_2, silica gel, 0–10°, 100% yield.[2]

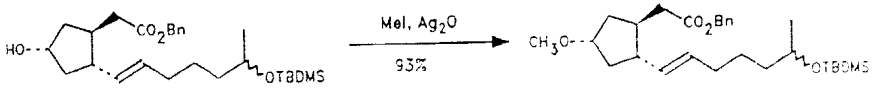


Ref. 3

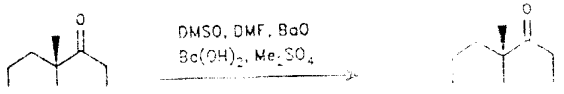
3. CH_2N_2, HBF_4, CH_2Cl_2, Et_3N, 25°, 1 h, 95% yield.[4,5]
4. MeI, solid KOH, DMSO, 20°, 5–30 min, 85–90% yield.[6]
5. $(MeO)_2POH$, cat. TsOH, 90–100°, 12 h, 60% yield.[7]
6. $Me_3O^+BF_4^-$, 3 days, 55% yield.[8]
7. CF_3SO_3Me, CH_2Cl_2, Pyr, 80°, 2.5 h, 85–90% yield.[9]
8. Because of the increased acidity and reduced steric requirement of the carbohydrate hydroxyl, *t*-BuOK can be used as a base to achieve ether formation.[10]



9. MeI, Ag_2O, 93% yield.[11]



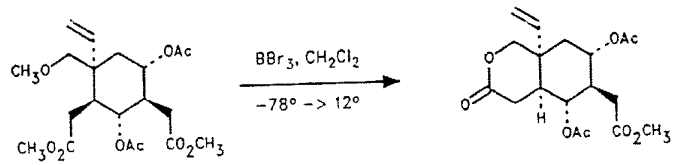
10. Me_2SO_4, DMSO, DMF, $Ba(OH)_2$, BaO, rt, 18 h, 88% yield.[12]



11. MeI or Me_2SO_4,[13] NaH or KH, THF. This is the standard method for introducing the methyl ether function onto hindered and unhindered alcohols.

Cleavage

1. Me_3SiI, $CHCl_3$, 25°, 6 h, 95% yield.[14] A number of methods have been reported in the literature for the *in situ* formation of Me_3SiI[15] since Me_3SiI is somewhat sensitive to handle. This reagent also cleaves many other ether-type protective groups, but selectivity can be maintained by control of the reaction conditions and the inherent rate differences between functional groups.
2. BBr_3, NaI, 15-crown-5.[16] Methyl esters are not cleaved under these conditions.[17]
3. BBr_3, EtOAc, 1 h, 95% yield.[18]
4. BBr_3, CH_2Cl_2, high yields.[19]



This method is probably the most commonly used method for the cleavage of ethers because it generally gives excellent yields with a variety of structural types. BBr_3 will cleave ketals.

5. $BF_3 \cdot Et_2O$, $HSCH_2CH_2SH$, HCl, 15 h, 82% yield.[20,21]
6. $MeSSiMe_3$ or $PhSSiMe_3$, ZnI_2, $Bu_4N^+I^-$.[22] In this case the 6-*O*-methyl ether was cleaved selectively from permethylated glucose.
7. $SiCl_4$, NaI, CH_2Cl_2, CH_3CN, 80–100% yield.[23]
8. AlX_3 (X = Br, Cl), EtSH, 25°, 0.5–3 h, 95–98% yield.[24]
9. *t*-BuCOCl or AcCl, NaI, CH_3CN, 37 h, rt, 84% yield.[25] In this case the methyl ether is replaced by a pivaloate or acetate group that can be hydrolyzed with base.
10. Ac_2O, $FeCl_3$, 80°, 24 h.[26] In this case the methyl ether is converted to an acetate. The reaction proceeds with complete racemization.
11. AcCl, NaI, CH_3CN.[27]

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Substituted Methyl Ethers

2. Methoxymethyl Ether (MOM Ether): CH_3OCH_2–OR (Chart 1)

Formation

1. CH_3OCH_2Cl, NaH, THF, 80% yield.[1]
2. CH_3OCH_2Cl, *i*-Pr_2NEt, 0°, 1 h → 25°, 8 h, 86% yield.[2] This is the most commonly employed procedure for introduction of the MOM group. The [illegible]chloromethyl methyl ether is reported to be carcinogenic.